METHOD AND APPARATUS FOR MODULATING CELLULAR METABOLISM DURING POST-ISCHEMIA OR HEART FAILURE

Field of the Invention

This document generally relates to cardiac rhythm management systems and particularly, but not by way of limitation, to such systems modulating cardiac cellular metabolism with drug delivery.

Background

A heart is the center of a person's circulatory system. It includes a complex electro-mechanical system performing two major pumping functions. The left portions of the heart, including the left atrium and the left ventricle, draw oxygenated blood from the lungs and pump it to the organs of the body to provide the organs with their metabolic needs for oxygen. The right portions of the heart, including the right atrium and the right ventricle, draw deoxygenated blood from the organs and pump it into the lungs where the blood gets oxygenated. These pumping functions are accomplished by cardiac contractions, i.e., contractions of the myocardium (heart muscles).

Cardiac cells produces the energy required for the cardiac contractions from free fatty acids and glucose via aerobic metabolism. The energy production from glucose is more oxygen efficient than the energy production from fatty acids. In a normal adult heart, about 60-90% of the energy is produced from fatty acid oxidation. If the heart becomes ischemic, blood flow to the heart is reduced, resulting in insufficient oxygen supplying the aerobic metabolism of cardiac cells. In decompensated heart failure, glucose oxidation becomes the primary source of energy produced by the aerobic metabolism. During ischemia and compensated heart failure, fatty acids are still the primary source of energy, even though it is less oxygen-efficient than glucose. In both situations, the heart fails to maintain the normal rate of metabolism because of the reduced availability of oxygen. This results in a reduction of myocardial contractility, and hence, reduction of the heart's pumping efficiency and thus diminished blood flow.

Therefore, as a treatment for ischemia and heart failure, as well as related conditions and symptoms, there is a need to increase the rate of metabolism in cardiac cells in response to the reduced availability of oxygen.

Summary

A drug delivery system detects a cardiac condition indicative of a need for increasing a cardiac metabolic level and, in response, releases a drug into tissue or blood to shift a source of metabolically synthesized energy fueling cardiac contraction from fatty acid to glucose. Such a system is applied to treat, for example, a patient suffering ischemia and/or heart failure or a patient having suffered myocardial infarction.

In one embodiment, a system includes a transdermal drug delivery device, an implantable cardiac rhythm management (CRM) device, and an external device. The implantable CRM device communicates with the transdermal drug delivery device and includes an ischemia detector, a drug level detector, and a drug delivery controller. The ischemia detector produces an ischemia indicating signal upon detection of an ischemia. The drug level detector detects a drug concentration in blood and produces an indication of the blood drug concentration. The external device communicates with the implantable CRM device and includes an external user input to receive an external user command. The drug delivery controller of the implantable CRM device controls the transdermal drug delivery device based on at least one of the ischemia indicating signal, the indication of the blood drug concentration, and the external user command.

In one embodiment, a system includes an implantable metabolic sensor, an implantable processor, and an implantable drug delivery device. The implantable metabolic sensor senses a metabolic signal indicative of a cardiac metabolic level. The implantable processor includes a metabolic sensor processing circuit and a drug delivery controller. The metabolic sensor processing circuit determines the cardiac metabolic level from the metabolic signal. The drug delivery controller produces a drug delivery signal based on the cardiac metabolic level. The implantable drug delivery device communicates with the implantable processor and delivers a drug in response to

the drug delivery signal. The implantable drug delivery device includes a drug reservoir storing a drug shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose.

In one embodiment, an implantable CRM device executing an automated ischemia detection algorithm is used to detect an ischemia. The implantable CRM device also detects an external user command directing a drug delivery. The external user command is transmitted from an external device. A drug delivery signal is produced upon a detection of at least one of the ischemia and the external user command. The drug delivery signal is transmitted to an transdermal drug delivery device. In response, a drug is delivered from the transdermal drug delivery device.

In one embodiment, a metabolic signal is sensed using an implantable sensor. A cardiac metabolic level is determined based on the metabolic signal using an implantable processor. A drug delivery signal is produced based on the cardiac metabolic level. The drug delivery signal is transmitted from the implantable processor to an implantable drug delivery device. In response, the implantable drug delivery device delivers a drug to shift a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose.

This Summary is an overview of some of the teachings of the present application and not intended to be an exclusive or exhaustive treatment of the present subject matter. Further details about the present subject matter are found in the detailed description and appended claims. Other aspects of the invention will be apparent to persons skilled in the art upon reading and understanding the following detailed description and viewing the drawings that form a part thereof, each of which are not to be taken in a limiting sense. The scope of the present invention is defined by the appended claims and their equivalents.

Brief Description of the Drawings

In the drawings, which are not necessarily drawn to scale, like numerals describe similar components throughout the several views. The drawings illustrate generally, by way of example, but not by way of limitation, various embodiments discussed in the present document. The drawing are for illustrative purposes only and not to scale nor anatomically accurate.

FIG. 1 is an illustration of an embodiment of a transdermal drug delivery system and portions of an environment in which it is used.

FIG. 2 is a block diagram showing one embodiment of the circuit of portions of the transdermal drug delivery system such as shown in FIG. 1.

FIG. 3 is a flow chart illustrating an embodiment of a method for delivering a cardiac metabolism drug using the transdermal drug delivery system such as shown in FIG. 1.

FIG. 4 is an illustration of an embodiment of an implantable drug delivery system and portions of an environment in which it is used.

FIG. 5 is a block diagram showing one embodiment of the circuit of portions of the implantable drug delivery system such as shown in FIG. 4.

FIG. 6 is an illustration of another embodiment of an implantable drug delivery system and portions of an environment in which it is used.

FIG. 7 is a block diagram showing one embodiment of the circuit of portions of the implantable drug delivery system such as shown in FIG. 6.

FIG. 8 is a flow chart illustrating an embodiment of a method for delivering a cardiac metabolism drug using one of the implantable drug delivery systems such as shown in FIGS. 4 and 6.

Detailed Description

In the following detailed description, reference is made to the accompanying drawings which form a part hereof, and in which is shown by way of illustration specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention,

and it is to be understood that the embodiments may be combined, or that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing from the spirit and scope of the present invention. The following detailed description provides examples, and the scope of the present invention is defined by the appended claims and their equivalents.

It should be noted that references to "an", "one", or "various" embodiments in this disclosure are not necessarily to the same embodiment, and such references contemplate more than one embodiment.

Cardiac contraction is fueled by energy synthesized aerobically by cardiac cells from energy sources including glucose and free fatty acids. In normal adult hearts, the majority of the energy is produced from fatty acid oxidation. However, in certain cardiac disorders, decompensated heart failure for example, glucose becomes the primary energy source for aerobic metabolism. During ischemia and compensated heart failure, fatty acids are still the primary energy source even though fatty acids are less oxygen efficient than glucose. Pharmaceutical agents which shift metabolism from fatty acid oxidation to glucose oxidation are beneficial in patients with ischemia or heart failure, and, when administered chronically, are beneficial in heart failure or post-myocardial infarction patients. These pharmaceutical agents are generally most effective when administered in response to certain physiological signals and/or events, such as a change in cardiac metabolic level and/or an ischemic event. This is achieved by using a drug delivery system that detects the certain physiological signals and/or events and, in response, delivers one or more pharmaceutical agents that shift cardiac metabolism from fatty acid oxidation to glucose oxidation. The term "pharmaceutical agents," as used in this document, include agents that are chemical, biochemical, and/or biologic in nature.

Such a drug delivery system can be employed to deliver pharmaceutical agents to treat acute events, for instance, for relief of angina or heart failure decompensation, or to deliver pharmaceutical agents chronically to treat compensated heart failure or left ventricular dysfunction, or prophylactically to patients having previously suffered myocardial infarction. The pharmaceutical agents act upon cardiac cells to decrease the

oxygen requirements to fuel cardiac metabolism by, for example, inhibiting or reducing fatty acid oxidation and/or increasing, enhancing, or stimulating pyruvate, glucose or lactate oxidation, preferably in cardiac cells. By decreasing the oxygen requirement for maintaining a normal or tolerable rate of cardiac metabolism by increasing its oxygen efficiency, the drug delivery system can be employed to minimize necrosis and apoptosis during chronic ischemia or an ischemic event.

In one embodiment, pharmaceutical agents within the scope of the present subject matter include, but are not limited to, those which shift metabolism from fatty acid oxidation to glucose oxidation, e.g., agents which decrease, inhibit (suppress) or reduce fatty acid oxidation (trimetazidine or ranolazine), and/or increase, enhance or stimulate pyruvate, glucose or lactate oxidation, preferably in cardiac cells. Thus, agents which inhibit lipolysis (nicotonic acid, aka niacin, and beta-adrenergic receptor antagonists), the rate of fatty acid release from fat cells, lower plasma fatty acid concentrations, uptake of fatty acids by the heart, entrance of fatty acids into the mitochodrion, for instance, by inhibiting CPT-1 (carnitine, L-propionylcarnitine, perhexiline, etoxomir, or oxfenicine), or inhibit the levels or activity of acyl-CoA dehydrogenase, e.g., long chain or medium chain acyl-CoA dehydrogenase, enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase, or beta-ketothiolase, or enhance the levels or activity of pyruvate dehydrogenase, e.g., dichlororacetate inhibits pyruvate dehydrogenase kinase, and increases cytosolic acetyl-CoA, which inhibits fatty acid oxidation, glucose (insulin) and/or lactate transporters or otherwise alter glucose transport (Akt-1) or stimulates insulin secretion (GLP-1). Acetyl CoA is converted to malonyl CoA, which inhibits carnitine palmitoyltransferase-1 (CPT-1), thereby reducing fatty acid uptake into mitochondria.

Those agents may be employed alone or in conjunction with other agents such as anti-hypertensive agents, anti-arrhythmic agents, pressors, vasopressors, vasodilators, anti-hyperlipidemic agents, anti-anginal agents, ionotropic agents, diuretics, volume expanders, thrombolytics, anti-platelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers, or any combination thereof, including but not limited to diuretics such as thiazides, e.g., hydrochlorothizide,

loop duretics, e.g., furosemide, and potassium-sparing agents, e.g., amiloride, sprionolactone and triamterene and hydrochlorothiazide, beta-blockers such as bisoprolol, carvedilol, labetolol and metoprolol, angiotensin-converting enzyme inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, delapril, pentopril, moexipril, spirapril, temocapril, and imidapril, calcium channel blockers, alpha blockers, angiotensin II antagonists, e.g., losartan, statins, e.g., atorvastatin, pitavastatin, and pravastatin, or other lipid lowering agents, moxonidine, dihydropyridines, e.g., amlodipine, class III and IV antiarrhythmics, e.g., amiodarone, azimilide, sotalol, dofetilide, and ubutilide, aspirin, selective non-adrenergic imidazoline receptor inhibitors, hebivolol, vasopeptidase inhibitors, e.g., fasidotritat, omapatrilat, samapatrilat, substrates, inhibitors or inducers of cytochrome P450 enzymes, lidocaine, warfarin, oligonucleotides (sense or antisense), natriuretic peptides such as ANP, BNP, NT pro BNP, CNP, and DNP, colforsin daropate hydrochloride (forskilin derivative), antagonists of platelet integrin IIb/IIIa receptors, e.g., abciximab and trofiblant, reteplase, P2 receptor antagonists, e.g., ticlopidine and clopidrogel, mibefradil, hirudin, acetylcholinesterase inhibitors, cardiac glycosides, e.g., digoxin and digitoxin, bradykinin, neutral endopeptidease inhibitors, e.g., neprilysin, direct-acting vasodilators, e.g., hydralazine, nitroglycerin, sodium nitroprusside, catecholamines, dobutramine and dopamine, phosphodiesterase inhibitors, e.g., amrinone and milrinone, TNFα, pentoxifylline, growth hormone, cytokine inhibitors, aldosterone receptor antagonists, calcium sensitizers, nesiritide, 3,5-dicodothyropropionic acid, etomoxir, endothelin receptor antagonists, chlorthiadone, doxazosin, nesiritide, cilostazol, rilmenidine, ticlopidine, dihydropines such as nifedipine and nisoldipine, timolol, propanolol, verapamil, diltiazem, lisinopril, noopept (N-phenylacetyl-L-polyglycine ethylester), cariporide, geldanamycin, radicicol, ibudilast, selective delta (1) agonists such as 2-methyl-4a-alpha-(3-hydroxy-phenyl)-1,2,3,4,4a,5,12,12a-alpha-octahydroquinolinol [2,3,3-g]isoquinoline, monophosphoryl lipid A, RC552, adenosine, adenosine receptor agonists, adenosine triphosphate sensitive channel openers, dipyridamole, fibroblast growth factor, atenolol, ezetimibe, lerosimendan, sirolimus, paclitaxil, actinomycin D, dexamethasone, tacrolimeus,

everolimus, estradiol, quinapril, tranilast, antiopeptin, trapidil, lacidipine, thiazolidinediones, fenofibrate, lacidipine, nebrivolol, nicotinic acid, probucal, rosuvastatin, gemfibrozil, glitazones, indobugen, alpha-tocopherol, dypiridamole, resins, e.g., cholestyramine and colestipol, bezafibrate, or listat, niacin, heparin, e.g., low molecular weight heparins such as dalteparin sodium and nadroparin calcium, bivalirucin, nitroglycerin, nicorandil, denopamine, eptifibatide, xemilofiban, or bofiban, trimetazidine, nicorandil, dalteparin, and isosorbide 5-mononitrate. Additional pharmaceutical agents may be considered based on evidence of their direct or indirect roles in preventing or reducing injury or hemodynamic compromise related to myocardial infarction and/or heart failure. Examples of such pharmaceutical agents include, but are not limited to, L-arginine; nitric oxide (NO); NO derivatives such as nitroxl anion (HNONO-) and peroxynitrite (ONOO-); iNOS, eNOS, and inhibitors such as nitro-L-arginine methyl ester; NO donors such as diethylamine (DEA) NO and nitroglycerin (NTG); and interleukins and interleukin inhibitors.

This document discusses, among other things, drug delivery systems each deliver a drug including one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose. Specific examples of the one or more pharmaceutical agents include, but are not limited to, all pharmaceutical agents discussed in this document.

FIG. 1 is an illustration of an embodiment of a transdermal drug delivery system 100 and portions of an environment in which it is used. System 100 includes, among other things, an implantable cardiac rhythm management (CRM) device 110, a transdermal drug delivery device 130, an external device 150, a remote device 170. As shown in FIG. 1, implantable CRM device is implanted in a body 102. Transdermal drug delivery device 130 is attached to the skin surface of body 102 at a site near heart 105. A lead system 108 provides electrical connection between heart 105 and implantable CRM device 110. A communication link 120 allows signal transmission between implantable CRM device 110 and transdermal drug delivery device 130. A telemetry link 140 provides for bidirectional communication between implantable CRM

device 110 and external device 150. A network 160 provides for bidirectional communication between external device 150 and remote device 170

System 100 allows a drug delivery to be triggered by any one of implantable CRM device 110, external device 150, and remote device 170. In one embodiment, implantable CRM device 110 triggers a drug delivery upon detecting a predetermined signal or condition. External device 150 triggers a drug delivery upon receiving an external user command from the patient wearing implantable CRM device 110 and transdermal drug delivery device 130 or from another person such as a relative, a friend, or a physician/caregiver. The patient enters the external user command when he or she detects an abnormal condition, such as a chest pain indicative of angina. Another person caring for the patient may also enter the external user command upon a request by the patient or an observation of an abnormal condition. Remote device 170 triggers a drug delivery upon receiving a remote user command from a physician/caregiver, who has been notified of the patient's condition. In other embodiments, external device 150 and/or remote device 170 process signals and/or a condition detected by implantable CRM device 110 to determine whether to trigger a drug delivery.

In one embodiment, system 100 is used for an acute treatment for relief of angina or heart failure decompensation. In another embodiment, system 100 is used to treat "silent myocardial infarctions" that are not detectable by the patient. A drug delivery is triggered upon detection of ischemia by implantable CRM device 110 and/or upon receiving an external user command from a patient in response to angina.

FIG. 2 is a block diagram showing one embodiment of the circuit of portions of system 100. Implantable CRM device 110 as shown in FIG. 2 includes pacing and defibrillation capabilities. In addition to drug delivery, examples of therapies delivered by implantable CRM device 110 include, but are not limited to, bradyarrhythmia pacing, anti-tachyarrhythmia pacing, atrial and/or ventricular cardioversion/defibrillation, cardiac resynchronization therapy, and cardiac remodeling control. However, the pacing and defibrillation capabilities are not necessary for system 100 to perform drug delivery, and hence, are not necessary elements of implantable CRM device 110. In other words, implantable CRM device 110 can be an

implantable pacemaker and/or defibrillator with additional functions including control of drug delivery, or it can be a dedicated implantable drug delivery processor or controller.

In one embodiment, implantable CRM device 110 includes a sensing circuit 211, an ischemia detector 212, a drug delivery controller 213, a drug level indicator 217, a pacing circuit 218, a defibrillation circuit 219, an implant controller 215, an implant communication module 222, and an implant telemetry module 242. Sensing circuit 211 senses an intracardiac electrogram through a lead of lead system 108. Ischemia detector 212 detects an ischemia and produces an ischemia indicating signal when a ischemic condition is detected. In one embodiment, ischemia detector 212 has an input connected to sensing circuit 211 and an ischemia analyzer running an automatic ischemia detection algorithm to detect an ischemic condition from the electrogram. One specific example of an electrogram-based ischemia detector 212 is discussed in Zhu et al., U.S. Patent Application No. 09/962,852, entitled "EVOKED RESPONSE SENSING FOR ISCHEMIA DETECTION," filed on September 25, 2001, assigned to Cardiac Pacemakers, Inc., which is incorporated herein by reference in its entirety. In another embodiment, ischemia detector 212 includes an electrical impedance based sensor using a low carrier frequency (e.g. 100 Hz) and an ischemia analyzer running an automatic ischemia detection algorithm to detect an ischemic condition from the electrical impedance signal. Tissue electrical impedance has been shown to increase significantly during ischemia, as discussed in Min, et al. International Journal of Bioelectromagnetism, 5(1): 53-56 (2003). Ischemia detector 212 senses low frequency electrical impedance signal between electrodes interposed in the heart, and detects the ischemia as abrupt changes in impedance (such as abrupt increases in value). In yet another embodiment, ischemia detector 212 includes a local heart motion based sensor utilizing an accelerometer located within a lead body positioned on or in the heart and an ischemia analyzer running an automatic ischemia detection algorithm to detect an ischemic condition from the acceleration signal. Ischemia detector 212 detects ischemia as an abrupt decrease in the amplitude of local cardiac accelerations. Upon receiving at least one of the ischemia indicating signal from ischemia detector

212, an external user command from external device 150, and a remote user command from remote device 170, drug delivery controller 213 generates a drug delivery signal. The drug delivery signal is transmitted through communication link 120 to transdermal drug delivery device 130 to trigger a drug delivery. After the drug delivery, drug level indicator 217 measures or estimates a blood drug concentration of the drug delivered to produce an indication of the blood drug concentration. In one embodiment, drug level indicator 217 includes a drug level detector that measures the blood drug concentration. In another embodiment, drug level indicator 217 includes a sensor measuring a physiological parameter indicative of the blood drug concentration. Examples of such a sensor include a respiration sensor and a heart rate detector. If drug level indicator 217 produces an indication of a blood drug concentration that is below a predetermined minimum level, drug delivery controller 213 produces a drug delivery signal to continue the drug delivery or start another drug delivery. Implant controller 215 provides for overall control and signal processing for implantable CRM device 110. Implant communication module 222 provides for a signal transmission interface allowing implantable CRM device 110 to communicate with transdermal drug delivery device 130, such as to transmit the drug delivery signal, via communication link 120. Implant telemetry module 242 provides for a telemetry interface allowing implantable CRM device 110 to communicate with external device 150 via telemetry link 140.

Lead system 108 includes one or more pacing leads, defibrillation leads, pacing-defibrillation leads, or any combination of such leads. It allows sensing of electrical signals from heart 105 and/or delivery of pacing pulses and/or defibrillation shocks to heart 105. In one embodiment, lead system 108 includes one or more transvenous leads each having at least one sensing-pacing electrode disposed within heart 105. In one embodiment, lead system 108 includes one or more epicardial leads each having at least one sensing-pacing electrode disposed on heart 105. On one embodiment, lead system 108 includes one or more leads each having at least one sensor such as an accelerometer or a metabolic sensor. In one specific embodiment, lead system 108 includes one or more leads each having a metabolic sensor disposed in a blood pool when the lead is implanted.

Transdermal drug delivery device 130 includes electrodes 232A-B, drug reservoir 234, drug delivery device controller 236, drug delivery status indicator 238, and drug delivery communication module 224. One specific example of transdermal drug delivery device 130 is discussed in Scheiner et al., U.S. Patent No. 6,361,522, entitled "DRUG DELIVERY SYSTEM FOR IMPLANTABLE CARDIAC DEVICE," assigned to Cardiac Pacemakers, Inc., which is incorporated herein by reference in its entirety. In one embodiment, transdermal drug delivery device 130 is a skin patch allowing electrically controlled transdermal drug delivery by, for example, iontophoresis, electroporation, electrorepulsion, or electro-osmosis. The skin patch is to be attached on a surface site of body 102 near heart 105. Electrodes 232A and 232B are skin-contact electrodes. Drug reservoir 234 contains the drug, which includes one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose. Drug delivery status indicator 238 allows the patient and any other person such as a physician/caregiver to monitor, for example, whether the drug is being delivered and/or the amount of the drug remains in drug reservoir 234. Drug delivery device controller 236 controls the overall operation of transdermal drug delivery device 130. In one embodiment, drug delivery device controller 236 generates an electrical potential to cause the drug delivery upon receiving and/or decoding the drug delivery signal. Drug delivery communication module 224 provides for a signal transmission interface allowing transdermal drug delivery device 130 to communicate with implantable CRM device 110, such as to receive the drug delivery signal, via communication link 120.

Communication link 120 is supported by implant telemetry module 222 and drug delivery communication module 224. It allows communications between implantable CRM device 110 and transdermal drug delivery device 130. In one embodiment, communication link 120 is a telemetry link. In another embodiment, implantable CRM device 110 transmits electrical signals representative of the drug delivery signal into tissue of body 102, to be sensed through electrodes 232A-B and hence received by transdermal drug delivery device 130. In this embodiment, communication link 120 uses body 102 as the conductive medium for conducting

electrical signals. One specific example of such a communication link is discussed in Sweeney et al., U.S. Patent Application No. 09/740,129, entitled "DRUG DELIVERY SYSTEM FOR IMPLANTABLE MEDICAL DEVICE," filed on December 18, 2000, assigned to Cardiac Pacemakers, Inc., which is incorporated herein by reference in its entirety.

External device 150 includes an external user input 252, an external display 254, an external device controller 256, an external telemetry module 244, and an external network interface 262. External user input 252 receives the external user command from the patient or another person. In a further embodiment, it also receives other commands or instructions to control the operation of transdermal drug delivery device 130 and/or implantable CRM device 110. External device 150 transmits the external user command to implantable CRM device 110, resulting in a production of the drug delivery signal by drug delivery controller 213. In one embodiment, external device 150 also transmits the external user commands to remote device 170. In response, a remote user command directing a drug delivery may return from remote device 170. External device 150 relays the remote user command to implantable CRM device 110, resulting in a production of the drug delivery signal by drug delivery controller 213. External user input 252 includes a switch. In one embodiment, external user input 252 includes a push button. The patient pushes it, for example, when feeling a chest pain indicative of angina. In another embodiment, external user input 252 includes a voice controlled switch such that the patient may orally order a drug delivery. External telemetry module 244 provides for a telemetry interface allowing external device 150 to communicate with implantable CRM device 110 via telemetry link 140. External network interface 262 provides for a network interface allowing external device 150 to communicate with remote device 170 via network 160.

Telemetry link 140 is a wireless bidirectional data transmission link supported by implant telemetry module 242 and external telemetry module 244. In one embodiment, telemetry link 140 is an inductive couple formed when two coils – one connected to implant telemetry module 242 and the other connected to external telemetry module 244 – are placed near each other. In this embodiment, the patient or

another person places external device 150 on body 102 over implantable CRM device 110. In another embodiment, telemetry link 140 is a far-field radio-frequency telemetry link allowing implantable CRM device 110 and external device 252 to communicate over a telemetry range that is at least ten feet.

Remote device 170 includes an emergency response module 272, a remote signal processor 274, a remote user interface 276, a remote device controller 278, and a remote network interface 264. By executing one or more predetermined algorithms, remote signal processor 274 processes signals transmitted from external device 150 and signals transmitted from implantable CRM device 110. Emergency response module 272 contacts an emergency response unit, such as by calling 911 (in the United States), in response to an emergency situation as determined by one of implantable CRM device 110, external device 150, and remote device 170. In one embodiment, external device 150 transmits the external user command to remote device 170 as a request for contacting the emergency response unit through emergency response module 272. In another embodiment, remote signal processor 274 analyzes signals acquired by implantable CRM device 110 and transmitted to remote device 170, such as a portion of the electrogram sensed by sensing circuit 211, to determine the need for contacting the emergency response unit. In yet another embodiment, a physician/caregiver observes signals and/or the result of the analysis through remote user interface 276 to determine whether to contact the emergency response unit. Remote user interface 276 allows the physician/caregiver to enter a remote user command to be transmitted to transdermal drug delivery device 130. It also allows physician/caregiver to enter the remote user command to be transmitted to implantable CRM device 110 for a delivery or adjustment of pacing and/or defibrillation therapy. Remote device controller 278 controls the overall operation of remote device 170. In one embodiment, remote device controller 278 generates commands controlling one or more of transdermal drug delivery device 130, implantable CRM device110, and external device 150 based on the received signals such as the portion of electrogram and the external user command. In one embodiment, remote device controller 278 executes an automatic algorithm to determine whether to issue a drug delivery command or to issue an electrical therapy

(pacing and/or defibrillation, including cardiac resynchronization and/or remodeling control) command, such as when a physician/caregiver is not immediately available. Remote network interface 264 provides for an interface allowing communication between remote device 170 and external device 150 via network 160.

Network 160 provides long distance bi-directional communication between external device 150 and remote device 170. It allows management of multiple implantable devices, such as implantable CRM device 110 and transdermal drug delivery device 130, from a central facility at a remote location. In one embodiment, this allows prompt response by a physician/caregiver at the central facility as demanded by the condition of a patient. In one embodiment, network 160 is based on a wireless communications system. In another embodiment, network 160 is based on a wired communications system. In one embodiment, network 160 utilizes portions of a standard communications system such as the Internet, a telephone system, or a radio frequency telemetry system.

FIG. 3 is a flow chart illustrating an embodiment of a method for delivering a drug using system 100. In one embodiment, the drug includes the one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose, and the method is used as an acute treatment for relief of angina or heart failure decompensation. The method can also be used to treat "silent myocardial infractions" that are not detectable by the patient.

Sensing circuit 211 senses at least one electrogram from heart 105 at 300. Ischemia detector 212 detects an ischemia at 310, by executing an automated ischemia detection algorithm. In one embodiment, ischemia detector 212 detects an ischemia by executing an automated ischemia detection algorithm that analyzes the electrogram. When an ischemia is detected, ischemia detector 213 produces an ischemia indicating signal and sends it to drug delivery controller 213.

External user input 252 receives an external user command at 320. The patient enters the external user command by in response to chest pain indicative of angina. Alternatively, another person, such as a physician/caregiver, an attendant, or a relative, enter the external user command after determining that the patient should receive an

immediate drug therapy. After external device 150 transmits the external user command to implantable CRM device 110, drug delivery controller 213 detects the external user command.

In one embodiment, in addition to transmitting the external user command to implantable CRM device 110, external device 150 transmits the external user command to remote device 170 though network 160 at 332. In one embodiment, remote device 170 also receives signals acquired by implantable CRM device 110, such as the electrogram, and transmits the signals to remote device 170 at 334. In one embodiment, after receiving the external user command and/or analyzing the signals acquired by implantable CRM device 110, remote device 170 notifies an emergence response unit, such as by calling 911 (as in the United States), at 336. In one embodiment, after receiving the external user command and/or analyzing the signals acquired by implantable CRM device 110, remote device 170 automatically produces a remote drug delivery command that is transmitted to implantable CRM device 110 through external device 150 at 335. In one embodiment, after receiving the external user command and/or analyzing the signals acquired by implantable CRM device 110, remote device 170 also notifies a user such as a physician/caregiver at 338. After the user makes a decision, remote device 170 receives a remote user command at 340. The remote user command directs a drug delivery and/or a delivery or adjustment of pacing (including such as cardiac resynchronization and remodeling control) or defibrillation therapy. Remote device 170 transmits the remote to external device 150 through network 160, and external device 150 relays the remote user command to implantable CRM device 110 at 342. Drug delivery controller 213 of implantable CRM device 110 detects the remote user command at 350.

Drug delivery controller 213 produces a drug delivery signal at 360, upon the detection of at least one of the ischemia, the external user command, the remote drug delivery command, and the remote user command. In one embodiment, the drug delivery signal is also transmitted to remote device 170 for notifying the emergency response unit and/or the user. Implantable CRM device 110 transmits the drug delivery signal to transdermal drug delivery device 130 at 370. In one embodiment, implantable

CRM device 110 transmits the drug delivery signal the drug delivery signal via a telemetry link between implantable CRM device 110 and transdermal drug delivery device 130. In another embodiment, implantable CRM device 110 transmits an electrical signal representing the drug delivery signal to transdermal drug delivery device 130 via tissue conduction. In one specific embodiment, implantable CRM device 110 transmits a voltage signal representing the drug delivery signal into tissue of body 102 to be detected by transdermal drug delivery device 130.

In response to the drug delivery signal, transdermal drug delivery device 130 delivers a drug into tissue at 380. The drug includes one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose. Then, drug level indicator 217 verifies that a sufficient amount of the drug has been delivered at 390, by detecting a signal indicative of a blood drug concentration. In one embodiment, this includes measuring a blood drug concentration directly. In another embodiment, this includes sensing a respiratory signal or measuring a heart rate. If drug level indicator 217 indicates that the blood drug concentration is below a predetermined level at 395, it produces an insufficiency alert signal and transmits it to drug delivery controller 213. Upon detection of the insufficiency alert signal, drug delivery controller 213 produces an additional drug delivery signal, and steps 360 – 395 are repeated until the drug level indicator 217 indicates that the blood drug concentration reaches the predetermined level at 395, or until a predetermined maximum dosage is reached.

FIG. 4 is an illustration of an embodiment of an implantable drug delivery system 400 and portions of an environment in which it is used. System 400 includes an implantable CRM device 410, which includes a drug delivery capability, and a drug eluting lead system 408. Identical numerals appearing in both FIGS. 1 and 4 indicate corresponding system components included in systems 100 and 400 that are structurally substantially identical.

System 400 allows a drug delivery to be triggered by any one of implantable CRM device 410, external device 150, and remote device 170. In one embodiment, implantable CRM device 410 triggers a drug delivery upon detecting a predetermined

signal or condition. External device 150 triggers a drug delivery upon receiving an external user command from the patient wearing implantable CRM device 410 or from another person caring for the patient. Remote device 170 triggers a drug delivery upon receiving a remote user command from a physician/caregiver. In other embodiments, external device 150 and/or remote device 170 process signals and/or condition detected by implantable CRM device 410 to determine whether to trigger a drug delivery.

In one embodiment, system 400 is used for a chronic treatment for compensated heart failure or left ventricular dysfunction. In another embodiment, system 400 is used for a chronic treatment of patients having suffered myocardial infarction. A drug delivery is triggered upon detection that a change in the cardiac metabolic level exceeds a predetermined threshold. In one embodiment, a drug delivery is triggered upon detection that a change in the BNP level exceeds a predetermined threshold.

FIG. 5 is a block diagram showing one embodiment of the circuit of portions of system 400. While implantable CRM device 410 as shown in FIG. 5 includes pacing and defibrillation capabilities, such capabilities are not necessary for system 400 to perform drug delivery, and hence, are not necessary elements of implantable CRM device 410. In other words, implantable CRM device 410 can be a pacemaker and/or defibrillator with additional functions including control of drug delivery, or it can be an implantable drug delivery device.

In one embodiment, to perform the drug delivery function, implantable CRM device 410 includes an implantable metabolic sensor 516, an implantable processor 595 including a metabolic sensor processing circuit 517 and drug delivery controller 513, and an implantable drug delivery device 590 including an implant drug reservoir 584 and a reservoir drug level detector 585. In the embodiment shown in FIG. 5, implantable processor 595 and implantable drug delivery device 590 are functional modules housed within the same implantable housing. Metabolic sensor 516 senses a metabolic signal indicative of a cardiac metabolic level (rate of metabolism of cardiac cells). Examples of metabolic sensor 516 include a pH sensor, an oxygen pressure (PO_2) sensor, a carbon dioxide pressure (PCO_2) sensor, a glucose sensor, a creatine sensor, a C-creative protein sensor, a creatine kinase sensor, a creatine kinase-MB

sensor, and any combination of such sensors. Metabolic sensor processing circuit 517 determines the cardiac metabolic level from the metabolic signal. Drug delivery controller 513 produces a drug delivery signal based on one or more of the cardiac metabolic level, the external user command, and the remote user command. Implant drug reservoir 584 contains the drug including the one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose. Reservoir drug level detector 585 monitors the amount of the drug remaining in implant drug reservoir 584 and produces a drug-level-low alert signal when the amount of the drug is below a predetermined level. The drug-level-low alert signal is transmitted to remote device 170 to inform a physician/caregiver.

Lead system 408 includes at least one drug eluting lead connected to implant drug reservoir 584. In one embodiment, the drug eluting lead includes a fluid passageway having one opening at one end of the lead connected to implant drug reservoir 584 and another opening connected to a drug eluting electrode at or near the other end of the lead that is to be disposed in or about heart 105. The fluid passageway allows fluid communication between implant drug reservoir 584 and the location to which the drug is released. In one embodiment, where implant CRM device 410 has pacing and/or defibrillation capability, lead system 408 includes one or more pacing leads, defibrillation leads, pacing-defibrillation leads, or any combination of such leads. At least one of these leads includes the fluid passageway allowing drug delivery. Thus, lead system 408 allows sensing of electrical signals from heart 105 and/or delivery of pacing pulses and/or defibrillation shocks to heart 105, as well as delivering drug to heart 105. In one embodiment, lead system 408 includes an endocardial lead including at least one drug eluting electrode configured to be disposed within one of a coronary sinus and a portion of a great cardiac vein adjacent to the left ventricle of heart 105. In another embodiment, lead system 408 includes an epicardial lead including at least one drug eluting electrode configured to be attached to a portion of an epicardial wall of heart 105. In one embodiment, metabolic sensor 516 is built-in or attached to a lead of lead system 408, such that when the lead is implanted, metabolic sensor 516 is in a blood pool.

Telemetry link 140, external device 150, network 160, and remote device 170 in system 400 are substantially identical to the identically numbered elements of system 100, except that the signals acquired by implantable CRM device and transmitted to remote device 170 include the metabolic signal and/or the cardiac metabolic level. Remote device controller 278 of remote device 170 generates commands controlling one or more of implantable CRM device 410, including metabolic sensor 516, implantable processor 595, and implantable drug delivery device 590, and external device 150 based on the received signals and the remote user command.

FIG. 6 is an illustration of an embodiment of another implantable drug delivery system 600 and portions of an environment in which it is used. System 600 includes an implantable CRM device 610, an implantable drug delivery device 690, and a communication link 620 between the two devices. Identical numerals appearing in both FIGS. 4 and 6 indicate corresponding system components included in systems 400 and 600 that are structurally substantially identical. In one embodiment, system 600 differs from system 400 by having the implantable drug delivery device physically separate from the implantable CRM device.

System 600 allows a drug delivery to be triggered by any one of implantable CRM device 610, external device 150, and remote device 170. In one embodiment, implantable CRM device 610 triggers a drug delivery upon detecting a predetermined signal or condition. External device 150 triggers a drug delivery upon receiving an external user command from the patient wearing implantable CRM device 610 and implantable drug delivery device 690 or from another person caring for the patient. Remote device 170 triggers a drug delivery upon receiving a remote user command from a physician/caregiver. In other embodiments, external device 150 and/or remote device 170 process signals and/or condition detected by implantable CRM device 610 to determine whether to trigger a drug delivery.

In one embodiment, system 600 is used as a chronic treatment for compensated heart failure or left ventricular dysfunction. In another embodiment, system 600 is used as a chronic treatment of patients having suffered myocardial infarction. A drug

delivery is triggered upon detection that a change in the cardiac metabolic level exceeds a predetermined threshold.

FIG. 7 is a block diagram showing one embodiment of the circuit of portions of system 600. While implantable CRM device 610 as shown in FIG. 5 includes pacing and defibrillation capabilities, such capabilities are not necessary for system 600 to perform drug delivery, and hence, are not necessary elements of implantable CRM device 610. In other words, implantable CRM device 410 can be a pacemaker and/or defibrillator with additional functions including control of drug delivery, or it can be an implantable processor dedicated to control of a separate implantable drug delivery device.

Implantable CRM device 610 generally retains implantable metabolic sensor 516 and implantable processor 595 of implantable CRM device 410, where implantable processor 595 includes a metabolic sensor processing circuit 517 and drug delivery controller 513. Implantable drug delivery device 590 of implantable CRM device 410 is replaced by a separate implantable device, that is, implantable drug delivery device 690.

Implantable drug delivery device 690 includes implant drug reservoir 584, reservoir drug level detector 585, implantable drug delivery device controller 736, and implantable drug delivery device communication module 724. Implantable drug delivery device controller 736 controls the overall operation of implantable drug delivery device 690. Implantable drug delivery device communication module 724 and an implant communication module 722 of implantable CRM device 610 support communication link 620. In one embodiment, communication link 620 is a telemetry link. In another embodiment, implantable CRM device 610 and transdermal drug delivery device 609 each transmit electrical signals into tissue of body 102, to be received by the other device through electrical conduction using tissue as the medium.

A drug eluting device 799 is connected to implant drug reservoir 584 to allow fluid communication between implant drug reservoir 584 and a body location to which the drug is released. In one embodiment, drug eluting device 799 includes at least one electrode connected to implant drug reservoir 584. In one specific embodiment, the

electrode is disposed in blood to allow the drug to be released to the blood. In another specific embodiment, the electrode is disposed in tissue to allow the drug to be diffused into tissue. In one embodiment, drug eluting device 799 allows electrically controlled drug delivery by, for example, iontophoresis, electroporation, electrorepulsion, or electro-osmosis. In one embodiment, drug eluting device 799 includes a porous polymer that is sensitive to electric field applied on it. The drug is embedded in the polymer. Implantable drug delivery device controller 736 controls the drug delivery by controlling the electric field applied to the polymer. A change in the electric filed changes the size of the pores in the polymer and/or the binding affinity of the polymer, resulting in the release of the drug.

Implantable drug delivery device 690 and drug eluting device 799 can be incorporated to another implantable device (other than implantable CRM device 610). In one embodiment, implantable drug delivery device 690 and drug eluting device 799 are incorporated into or attached onto a coronary stent. In one specific example, the coronary stent is placed near an electrode from which electrical stimuli are delivered, such as a pacing electrode of lead system 108. The electrical stimuli (e.g., pacing pulses) cause the drug to release from drug eluting device 799, in response to the changing electric field created by the electrical stimuli.

FIG. 8 is a flow chart illustrating an embodiment of a method for delivering a drug using either system 400 or system 600. In one embodiment, the drug includes the one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose, and the method is used as a chronic treatment of compensated heart failure or left ventricular dysfunction. The method can be applied to treat patients having previously suffered myocardial infarction.

Sensing circuit 211 senses at least one electrogram from heart 105 at 800. Metabolic sensor 516 senses a metabolic signal at 805. In one embodiment, metabolic sensor 516 senses one or more of a blood pH level, a blood oxygen pressure (PO_2), a blood carbon dioxide pressure (PCO_2), a blood glucose level, a blood creatine level, a blood C-creative protein level, a blood creatine kinase level, and a blood creatine

kinase-MB level. Metabolic sensor processing circuit 517 determines a cardiac metabolic level based on the metabolic signal, and detects a change in the cardiac metabolic level at 810. In one embodiment, metabolic sensor processing circuit 517 detects the change in the cardiac metabolism when the cardiac metabolic level exceeds a predetermined threshold. When the change in the cardiac metabolism is detected, metabolic sensor processing circuit 517 sends a signal indicative of the change to drug delivery controller 213.

In one embodiment, implantable CRM device 410 or 610 transmits the metabolic signal and/or the cardiac metabolic level to remote device 170 at 812. In one embodiment, this transmission is performed upon the detection of the change in the cardiac metabolism. In another embodiment, this transmission is performed in response to a request from remote device 170. In yet another embodiment, this transmission is performed on a predetermined schedule, such as on a periodic basis or when the patient is sleeping. In one embodiment, implantable CRM device 410 or 610 transmits additional acquired signals, such as a portion of the electrogram, to remote device 170 at 814. In one embodiment, after receiving the metabolic signal, the cardiac metabolic level, and/or the additional signals, remote device 170 notifies a user such as a physician/caregiver at 816. After the user makes a decision based on the signals received, remote device 170 receives a remote user command at 818. The remote user command directs a drug delivery and/or a delivery or adjustment of pacing or defibrillation therapy. Remote device 170 transmits the remote to external device 150 through network 160, and external device 150 relays the remote user command to implantable CRM device 410 or 610 at 820. Drug delivery controller 513 of implantable CRM device 410 or 610 detects the remote user command at 822.

Drug delivery controller 513 produces a drug delivery signal at 830, upon the detection of at least one of the changes in the cardiac metabolic level and the remote user command. In one embodiment with system 600, implantable CRM device 610 transmits the drug delivery signal to implantable drug delivery device 690 via telemetry or electrical conduction of the tissue intervening implantable CRM device 610 and implantable drug delivery device 690. In response to the drug delivery signal,

implantable CRM device 410 or implantable drug delivery device 690 delivers the drug into tissue at 840. In one embodiment, this includes delivering the drug through a drug eluting lead, such as the drug eluting endocardial lead or the drug eluting epicardial lead. In another embodiment, this includes delivering the drug through a drug eluting stent. The drug includes the one or more pharmaceutical agents shifting a source of metabolically synthesized energy for cardiac contractions from fatty acid to glucose. Then, implantable CRM device 410 or 610 verifies that a sufficient amount of the drug has been delivered at 850, by monitoring the cardiac metabolic level after the drug delivery. If the cardiac metabolic level is below a predetermined threshold at 855, drug delivery controller 513 produces an additional drug delivery signal, and steps 830 – 855 are repeated until the cardiac metabolic level reaches the predetermined level at 855.

Reservoir drug level detector 585 monitors the level of the drug remaining in implant drug reservoir 584 at 860. If reservoir drug level detector 585 determines that the level is below a predetermined low threshold at 870, it produces a drug-level-low alert signal. The drug-level-low alert signal is transmitted to remote device 170 at 880. Subsequently, remote device 170 notifies a physician/caregiver.

It is to be understood that the above detailed description is intended to be illustrative, and not restrictive. For example, transdermal drug delivery device 130 can substitute for implantable drug delivery device 690. Although the present therapy is described in the example of cardiac therapy, it is understood that many other applications are possible. Systems 100, 400, and 600 may be generally applied in drug delivery controlled by a condition detected or a signal sensed from a person. Other embodiments, including any possible permutation of the system components discussed in this document, will be apparent to those of skill in the art upon reading and understanding the above description. The scope of the invention should, therefore, be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled.